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Factor V Leiden Mutation Does Not Account for Central Venous Catheter-Related Thrombosis

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Indwelling central venous access devices are frequently associated with catheter-related thrombosis. The factor V Leiden gene mutation decreases the sensitivity of factor V to the anticoagulant activity of activated protein C, and has been shown to be the most common inherited defect associated with a hypercoagulable state. In this study, we sought to determine whether an increased prevalence of the factor V gene mutation could be identified in individuals with malignancies who had catheter-related thrombosis. Twenty-seven patients who had catheter-related thrombosis were identified and two (7%) tested positive for the heterozygous presence of the factor V gene mutation. Since the vast majority of patients with venous access devices who developed catheter-related thrombosis did *not* have the factor V gene mutation, pre-catheter placement testing for this mutation would have limited clinical utility. Am. J. Hematol. 58:150–152, 1998.

Key words: catheter-related venous thrombosis; factor V Leiden mutation; indwelling central venous access devices

INTRODUCTION

Indwelling central venous access devices are commonly used in cancer patients undergoing chemotherapy and in other patients requiring intermediate to long-term venous access [1]. These catheters provide access when peripheral veins are inadequate, facilitate administration of continuous infusion chemotherapy, and permit venous blood sampling. However, these catheters are associated with various complications including venous thrombosis. The prevalence of catheter-related thrombosis has most frequently been reported to be 10–20% [1,2]. Multiple variables have been studied as risk factors for catheter-related occlusions including type of catheter, catheter size, type of therapy, patient diagnosis, associated infection, position of catheter tip, and anesthesia used with insertion [1–4]. An additional patient characteristic that could be linked to catheter-related thrombosis has been identified, i.e., the factor V Leiden gene mutation [5,6]. This mutation, which results in decreased sensitivity of factor V to the anticoagulant activity of activated protein C, is the most common known inherited defect associated with a ''hypercoagulable state.''

The purpose of this study was to determine whether an increased prevalence of the factor V gene mutation could be identified in individuals with malignancies who had catheter-related thrombosis. We hypothesized that if an increased prevalence could be identified in such patients, then testing for the factor V mutation could be done prospectively to identify patients at increased risk for catheter-related thrombosis. This might affect patient selection for catheter placement or post-placement management, e.g., use of prophylactic anticoagulation.

METHODS

Twenty-eight patients with malignancy who had catheter-related thrombosis between September 1994 and August 1997 were retrospectively identified by hospital and clinic staff. Medical records were reviewed for patient demographics and descriptive details of the catheter-related thrombotic event. In addition, records of the 166 hematology/oncology patients who received venous access devices during 1996 were reviewed to identify any episodes of catheter-related thrombosis. In some pa-

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tients, the presence or absence of the factor V Leiden gene mutation had already been determined, but most patients gave informed consent to participate as required by our Institutional Review Board. Presence of the factor V Leiden gene mutation was determined by polymerase chain amplification [7].

RESULTS

Patient Characteristics

Patients ranged in age from 31 to 83 (median = 52 years); 26 patients were Caucasian, 2 African American; 8 were male, 20 female; 8 had hematologic malignancies, 20 solid tumors; 7 were receiving adjuvant chemotherapy and 21 chemotherapy for known malignancy. Patients had the following venous access devices: subcutaneous port, 17; tunneled external ''Hickman-type'' catheters, 6; larger pheresis catheters, 4; and peripheral central venous catheter, 1.

Catheter-Related Thromboses

Patients developed their thrombotic event from 1 week to 15 months (median = 2 months) after catheter insertion. Three patients had a history of prior thrombosis; 13 had received chemotherapy prior to the identification of the thrombotic event; 3 were receiving anticoagulants (1 heparin, 2 warfarin), and 3 had infections at the time of their thrombotic event. Twenty-three patients developed radiographically demonstrated evidence of thrombosis of the jugular, subclavian, or axillary veins. Two patients developed clinical evidence of venous thrombosis without radiographic documentation, and 3 patients developed system obstruction, i.e., inability to flush the line with radiographic demonstration of flow abnormalities associated with the catheter tip.

Of the 166 patients who received venous access devices during 1996, 12 (7.2%) developed catheter-related thromboses.

Factor V Leiden Gene Mutation

Two of the 27 patients tested (7%) (one patient refused) tested positive for the heterozygous presence of the factor V Leiden gene mutation. The patient characteristics and descriptive features of the thrombotic events in these two patients did not differ from those observed in patients without the gene mutation.

CONCLUSIONS

Only a slightly increased prevalence of the factor V Leiden gene mutation was identified in our patients who developed catheter-related venous thrombosis compared to the expected prevalence of approximately 5% in our largely ''Northern European Caucasian'' patient population [5–7]. The relatively small number of patients studied and our inability to test patients with venous access devices who did not develop catheter-related thrombosis limit our ability to draw rigorous conclusions. Nevertheless, since the vast majority (93%) of patients with venous thrombosis did *not* have the factor V Leiden gene mutation, this study provides support for the generally accepted concept that catheter-related thrombosis in patients with malignancy is primarily related to the mechanical presence of the catheter, i.e., alterations in venous blood flow, and to the well-recognized hypercoagulable state associated with malignancy. It also indicates that pre-catheter placement testing of patients with malignancy for the factor V Leiden mutation would have limited clinical utility.

It is worth emphasizing, however, that patients in our study who developed catheter-related thrombosis did so shortly after catheter placement, i.e., median = 2 months. Thus if the frequency of this complication, estimated in our 1996 patients to be 7.2%, and to be higher by others [1,2], is to be decreased, anticoagulation must be instituted at the time of catheter insertion. We are aware of only one published randomized, controlled trial of anticoagulant prophylaxis of catheter-related thrombosis [8]. Prophylactic fixed dose warfarin therapy reduced catheter-related thrombosis from 38 to 10% in patients who were given 1 mg of warfarin from 3 days before catheter placement until 90 days afterward. This low, fixed dose of warfarin did not prolong the prothrombin time and was not associated with bleeding complications [8]. Based on this study, prophylactic anticoagulation for patients with indwelling catheters has been recommended by the American Association of Chest Physicians [9]. The frequency of catheter-related thrombosis and the morbidity and cost associated with diagnosis and treatment of this complication lead us to support this recommendation for low-dose warfarin prophylaxis in all patients with indwelling central venous access devices.

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REFERENCES

1. Denny DF Jr: Placement and management of long-term central venous access catheters and ports. AJR 161:385–393, 1993.
2. Bothe A Jr, Lowell JA: Central venous catheter-related thrombosis. Surg Oncol Clin North Am 4:479–492, 1995.
3. Lemmers NWM, Gels ME, Sleijfer DTh, Plukker JTh, van der Graaf WTA, de Langen ZJ, Droste JHJ, Schraffordt Koops H, Hoekstra HJ: Complications of venous access ports in 132 patients with dissemi-

nated testicular cancer treated with polychemotherapy. J Clin Oncol 14:2916–2922, 1996.
4. Whitman ED: Complications associated with the use of central venous access devices. Curr Probl Surg 33:309–378, 1996.
5. Dahlbäck B: Inherited thrombophilia: Resistance to activated protein C as a pathogenic factor of venous thromboembolism. Blood 85:607–614, 1995.
6. Thomas DP, Roberts HR: Hypercoagulability in venous and arterial thrombosis. Ann Intern Med 126:638–644, 1997.
7. Beauchamp NJ, Daly ME, Hampton KK, Cooper PC, Preston FE, Peake IR: High prevalence of a mutation in the factor V gene within the UK population: Relationship to activated protein C resistance and familial thrombosis. Br J Haematol 88:219–222, 1994.
8. Bern MM, Lokich JJ, Wallach SR: Very low doses of warfarin can prevent thrombosis in central venous catheters. Ann Int Med 112:423–428, 1990.
9. Clagett GP, Anderson FA, Levine MN, et al: Prevention of venous thromboembolism. Chest 102(Suppl):391S–407S, 1992.